

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans¹⁻³

Abdul G Dulloo, Claudette Duret, Dorothee Rohrer, Lucien Girardier, Nouri Mensi, Marc Fathi, Philippe Chantre, and Jacques Vandermander

ABSTRACT

Background: Current interest in the role of functional foods in weight control has focused on plant ingredients capable of interfering with the sympathoadrenal system.

Objective: We investigated whether a green tea extract, by virtue of its high content of caffeine and catechin polyphenols, could increase 24-h energy expenditure (EE) and fat oxidation in humans.

Design: Twenty-four-hour EE, the respiratory quotient (RQ), and the urinary excretion of nitrogen and catecholamines were measured in a respiratory chamber in 10 healthy men. On 3 separate occasions, subjects were randomly assigned among 3 treatments: green tea extract (50 mg caffeine and 90 mg epigallocatechin gallate), caffeine (50 mg), and placebo, which they ingested at breakfast, lunch, and dinner.

Results: Relative to placebo, treatment with the green tea extract resulted in a significant increase in 24-h EE (4%; $P < 0.01$) and a significant decrease in 24-h RQ (from 0.88 to 0.85; $P < 0.001$) without any change in urinary nitrogen. Twenty-four-hour urinary norepinephrine excretion was higher during treatment with the green tea extract than with the placebo (40%, $P < 0.05$). Treatment with caffeine in amounts equivalent to those found in the green tea extract had no effect on EE and RQ nor on urinary nitrogen or catecholamines.

Conclusions: Green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se. The green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both. *Am J Clin Nutr* 1999;70:1040-5.

KEY WORDS Obesity, thermogenesis, catechins, polyphenols, caffeine, sympathetic nervous system, green tea, fat oxidation, catecholamines, men

INTRODUCTION

Fundamentally, there are only 2 ways to treat obesity: reduce energy intake or increase energy expenditure (EE). Because thermogenesis and fat oxidation are to a large extent under the control of the sympathetic nervous system (SNS), approaches that mimic or interfere with the SNS and its neurotransmitter norepinephrine offer a rational approach for obesity management (1-3). In this

context, there has been renewed interest in the potential thermogenic effects of many compounds extracted from plants (eg, caffeine from coffee and tea, ephedrine from ephedra, and capsaicin from pungent spices), largely because of their potential to modulate catecholamine release and activity (4). For example, capsaicin-rich foods (eg, chili peppers and red peppers) have been shown to stimulate fat oxidation and thermogenesis in humans (5, 6), and caffeine in relatively small amounts can potentiate thermogenesis induced by sympathetic stimuli, whether in response to cold, moderate exercise, or sympathomimetic drugs like ephedrine (7). In fact, long-term clinical trials have shown greater losses in body weight and body fat in obese patients treated with a combination of caffeine and ephedrine than in those treated with placebo, caffeine, or ephedrine alone (8).

Previous work in our laboratory, in which an *in vitro* system was used to measure the respiration rate of brown adipose tissue in rats, suggests that the interaction between caffeine and ephedrine resides in ephedrine's induced enhancement of sympathetic neural release of norepinephrine together with caffeine's ability to inhibit the phosphodiesterase-induced degradation of intracellular cyclic AMP (cAMP), and, to a lesser extent, caffeine's antagonism of the negative modulatory effect of adenosine on increased norepinephrine release (9). The net result, therefore, would be an elevated cellular concentration of cAMP—a critical intracellular mediator for the actions of catecholamines on thermogenesis. Apart from phosphodiesterases, adenosine, and certain prostaglandins, the concentration of norepinephrine at the synaptic junction and its interaction with adrenoceptors is also likely to be negatively modulated through its enzymatic degradation, namely by catechol *O*-methyltransferase (COMT) (10). Given

¹From the Department of Physiology, Faculty of Medicine, University of Geneva; Geneva University Hospital; and Laboratoires Arkopharma, Nice, France.

²Supported in part by Arkopharma Laboratories and by the Swiss National Science Research Fund.

³Address reprint requests to AG Dulloo, Institute of Physiology, University of Fribourg, Rue de Musée 5, CH-1700 Fribourg, Switzerland. E-mail: abdul.dulloo@unifr.ch.

Received December 16, 1998.

Accepted for publication March 31, 1999.

GREEN TEA AND THERMOGENESIS

1041

evidence that this enzyme can be inhibited by certain tea polyphenols (11), we recently investigated in our *in vitro* system whether an extract of green tea, by virtue of its high content of both caffeine and catechin polyphenols, could be an effective promoter of thermogenesis. These *in vitro* results (12) can be summarized as follows: 1) the green tea extract was found to be more effective than were equivalent amounts of caffeine in stimulating peripheral tissue thermogenesis, and 2) this difference between the green tea extract and equimolar caffeine in activating thermogenesis was much more marked under conditions of increased norepinephrine release because the synergistic interaction between the green tea extract and ephedrine on tissue thermogenesis was much more pronounced than that of caffeine or ephedrine.

On the basis of these *in vitro* data, our main objectives in this study were 2-fold: 1) to examine the extent to which daily administration of capsules containing a green tea extract (containing catechin polyphenols and caffeine in amounts comparable with those commonly consumed in green tea beverages in Asian communities) would stimulate thermogenesis and increase daily EE in humans, and 2) to determine whether the effects of the green tea extract on the metabolic rate and substrate oxidation in humans would be greater than that explained by its caffeine content *per se*.

SUBJECTS AND METHODS

Subjects

Healthy young men were recruited from the student and staff population of our University after complete medical and nutritional histories were obtained by use of a questionnaire. Smokers, competitive athletes, and persons who engaged in intense physical activities or who had a history of weight loss were not eligible for inclusion in the study. Inclusion criteria included body fatness ranging from lean to mildly obese (8–30% body fat). All selected subjects habitually consumed a typical Western diet, with fat contributing 35–40% of dietary energy intake, and their estimated intake of methylxanthines (mostly as caffeine-containing beverages) ranged from 100 to 200 mg/d. At the onset of the study, body weight and height were measured and body fat was determined by the method of Durnin and Wommersley (13) from measurements of skinfold thicknesses taken at 4 sites with a Harpenden skinfold caliper (British Indicators, Ltd, London); fat-free-mass (FFM) was calculated as the difference between body weight and body fat. Mean (\pm SEM) values for some of the physical characteristics of the 10 men participating in this study were as follows: age, 25 ± 1 y; height, 177 ± 3 cm; weight, 78.7 ± 4.3 kg; body mass index (BMI; in kg/m^2), 25.1 ± 1.2 ; percentage body fat, $18.2 \pm 1.8\%$; and FFM, 63.8 ± 2.5 kg. The study was approved by the Ethical Committee for Human Experimentation of the University of Geneva and was conducted in accordance with its rules and regulations.

Experimental design

Each subject spent 24 h in our respiratory chamber on 3 separate occasions and was randomly assigned to receive 1 of the following 3 treatments orally (in capsular form) 3 times/d (ie, 2 capsules with breakfast, lunch, and dinner): 1) a green tea extract containing 50 mg caffeine and 90 mg epigallocatechin gallate, 2) 50 mg caffeine, or 3) a placebo that consisted of cellulose as inert filler. The dosages represented the amount of caffeine and epigallocatechin gallate (the quantitatively most

important catechin polyphenol) in 2 capsules. The green tea extract (code name: AR25) was obtained by alcohol extraction from dry tea leaves of unfermented *Camellia sinensis*, standardized at 25% catechins, and commercially prepared in capsular form under the name Exolise (Arkopharma Laboratories, Nice, France). Note that apart from (–)-epigallocatechin gallate, the green tea extract also contains substantial amounts of other catechins: (–)-epigallocatechin, (–)-epicatechin, and (–)-epicatechin gallate. (–)-Epigallocatechin gallate constitutes $\geq 50\%$ of the total amount of tea catechins and is believed to be the most pharmacologically active tea catechin (14). In the present study, (–)-epigallocatechin gallate was found to constitute $\approx 72\%$ of total catechins, such that the amount of total catechins consumed with each meal was 125 mg. Consequently, ingestion of capsules containing the green tea extract AR25 provided daily a total of 150 mg caffeine and 375 mg catechins, of which 270 mg was epigallocatechin gallate. The various treatments in the respiratory chamber were administered in a double-blind design and with a 5–10-d interval between successive 24-h trials for each subject. During the entire study period (lasting 5–6 wk), the subjects were prescribed a weight-maintenance diet consisting of $\approx 13\%$ of energy as protein, $\approx 40\%$ as fat, and $\approx 47\%$ as carbohydrates. During each respiratory chamber trial, this diet was considered the "basal diet," which was fed at an energy level of 1.4 times the estimated basal energy requirements of the subject, predicted from the regression equation of Cunningham (15). Thus, during each of the subject's 3 respiratory chamber trials, the following conditions were the same: energy intake, nutrient composition of the diet, sedentary lifestyle pattern (reading, listening to radio, watching television, etc), pattern of physical activity, meal pattern, and time period for sleeping. No methylxanthine-containing foods or beverages were consumed 24 h before or during the stay in the respiratory chamber. During the first 8 h of each trial, the heart rate was monitored with a portable frequency meter.

Determination of daily energy expenditure and substrate oxidation

EE was continuously monitored by indirect calorimetry during the stay in the respiratory chamber, the details of which were described previously (16). The respiratory chamber had a large window overlooking the streets and was large enough (3 m long \times 2.5 m wide \times 2.5 m high) to provide the comforts of a hotel. It was furnished with a bed, resting armchair, table, wash basin and water tap, dry toilet, audiovisual equipment (television, video cassette recorder, radio, and tape recorder), intercom, and a telephone. The door was fitted with a double window as well as an air-lock system through which food and other items were provided. Complete privacy was obtainable by pulling a curtain over the windows. The chamber was sufficiently airtight to ensure that air left only through the apparatus that measures its flow rate and gas concentrations. A pump removed air continuously from the chamber at a rate that could be varied from between 50 and 100 L/min, which passed through a mass flow meter for continuous measurement of the flow rate. The effect of pumping air out resulted in air entering the chamber through a special inlet placed in the wall opposite the location where the air left. A fan ensured that the air was mixed inside the chamber and a thermostat ensured the maintenance of a constant and comfortable temperature. Air samples entering and leaving the chamber passed through differential analyzers for continuous

measurements of differences in oxygen and carbon dioxide contents between extracted air and inlet air. These data were continuously fed into an online computerized data acquisition system, from which EE and the respiratory quotient (RQ) were calculated throughout the measurement periods. Measurements were accurate within 1–2%, as described previously (16). The oxidation rates of protein, carbohydrate, and fat were calculated from 24-h EE, RQ, and urinary nitrogen excretion for each 24-h stay in the respiratory chamber (17).

Measurement of urinary nitrogen and catecholamines

During each subject's stay in the respirometer, urine was collected into 2 or more 2-L opaque glass containers (containing 10 mL of 5 mol HCl/L, each) over 2 periods to reflect diurnal and nocturnal phases, with the time intervals indicated below. After the 24-h collection period was complete, all urine samples were stored at -20°C until assayed for nitrogen with an autoanalyzer by the method of Kjeldahl and for epinephrine, norepinephrine, and dopamine concentrations by liquid chromatography with electrochemical detection.

Data presentation

EE, RQ, substrate oxidation, and urinary catecholamine data are reported as diurnal (corresponding to the first 15 h in the respiratory chamber, from 0800 to 2300), nocturnal (from 2300 to 0800 the next morning), and total 24-h values.

Statistics

Repeated-measures analysis of variance was used to determine significance. When statistically significant differences were detected, a post hoc pairwise comparison across treatments was performed by using Tukey's test. Significance was set at a P value < 0.05 . The statistical analyses were performed by using the computer software program STATISTIK 4.0 (Analytic Software, St Paul).

RESULTS

Energy expenditure

Mean (\pm SEM) diurnal, nocturnal, and total 24-h EE values are presented in Table 1. Significant differences across treatments were observed only for diurnal and total 24-h EE. Diurnal EE was higher during treatment with the green tea extract than during treatment with placebo or caffeine, by 4.5% and 3.2%, respectively, but significantly so only for the green tea extract. Total 24-h EE with the green tea extract, however, was significantly higher than that with both the placebo and caffeine, by 3.5% and 2.8%, respectively. There were no significant differences in diurnal, nocturnal, or total 24-h EE between the caffeine and placebo groups. Individual changes (relative to placebo) in total 24-h EE indicated an increase in only 2 subjects after caffeine treatment, but an increase in 6 of the 10 subjects after treatment with the green tea extract, ranging from 266 to 836 kJ (mean or median of ≈ 330 kJ). No correlation was observed between the magnitude of thermogenic response and the degree of fatness (BMI or percentage of body fat) of the subjects.

Respiratory quotient and substrate oxidation

RQs are shown in Table 2. Significant differences across treatments were found during the diurnal, nocturnal, and total

TABLE 1

Energy expenditure (EE) during diurnal, nocturnal, and total 24-h periods¹

	Placebo	Caffeine	Green tea	P ²
	kJ			
Diurnal EE	6463 \pm 386	6547 \pm 383	6754 \pm 352 ³	< 0.01
Nocturnal EE	3075 \pm 149	3053 \pm 148	3112 \pm 140	NS
Total 24-h EE	9538 \pm 521	9599 \pm 518	9867 \pm 488 ^{3,4}	< 0.01

¹ $\bar{x} \pm$ SEM; $n = 10$.

²For differences across treatments (ANOVA).

³Significantly different from placebo, $P < 0.05$ (post hoc pairwise comparison with Tukey's test).

⁴Significantly different from caffeine, $P < 0.05$ (post hoc pairwise comparison with Tukey's test).

24-h periods. Treatment with the green tea extract yielded significantly lower values than did the other 2 treatments during all 3 periods. Individual changes indicated that the RQ in most of the subjects (8 of 10) was substantially lower (differences > 0.01) after the green tea extract than after the placebo; in 4 of these subjects the difference was ≥ 0.04 . However, no correlation was observed between the magnitude of reduction in the RQ and the degree of fatness (BMI or percentage of body fat) of the subjects.

Because urinary nitrogen losses (and hence protein oxidation) indicated no significant differences across treatments for all 3 periods, the lower RQ during treatment with the green tea extract was due to a shift in substrate utilization in favor of fat oxidation. As indicated in Table 3, carbohydrate oxidation was significantly lower ($P < 0.01$) and fat oxidation was significantly higher ($P < 0.001$) after the green tea extract than after the placebo. By contrast, there were no significant differences in substrate oxidation between the caffeine and placebo groups. The relative contribution of protein, carbohydrate, and fat oxidation to daily EE are also presented in Table 3. The contribution of fat oxidation to 24-h EE during treatment with the green tea extract (41.5%) was significantly higher ($P < 0.001$) than during placebo treatment (31.6%).

Urinary excretion of catecholamines

Urinary excretion values of catecholamines during the study are shown in Table 4. Urinary epinephrine and dopamine were not significantly different across treatments in any of the 3 periods. Urinary norepinephrine and its precursor dopamine tended to be highest during treatment with the green tea extract, although differences across treatments were only significant for total 24-h norepinephrine.

Heart rate

None of the subjects reported any side effects and no significant differences in heart rates across treatments were observed during the first 8 h that the subjects were assessed in the respiratory chamber.

DISCUSSION

Although both coffee and tea are widely consumed worldwide, our knowledge of their influence on energy metabolism has been limited to studies of coffee or to its main pharmacologically active ingredient caffeine. Therefore, the results of the

GREEN TEA AND THERMOGENESIS

1043

TABLE 2

Respiratory quotient (RQ) during diurnal, nocturnal and total 24-h periods¹

	Placebo	Caffeine	Green tea	P ²
Diurnal RQ	0.887 ± 0.0081	0.878 ± 0.0071	0.858 ± 0.009 ¹	<0.002
Nocturnal RQ	0.870 ± 0.009	0.864 ± 0.008	0.841 ± 0.01 ¹	<0.01
Total 24-h RQ	0.881 ± 0.008	0.873 ± 0.007	0.852 ± 0.009 ¹	<0.001

¹ $\bar{x} \pm \text{SEM}$; $n = 10$.² For differences across treatments (ANOVA).³ Significantly different from placebo and caffeine, $P < 0.05$ (post hoc pairwise comparison with Tukey's test).

present investigation are the first to show in humans that tea (albeit green tea) also has the potential to influence EE and substrate utilization. Because dietary energy intake and diet composition were identical during all treatments and because the subjects maintained the same feeding and physical activity patterns during each 24-h respiratory chamber trial, the 4% increase in 24-h EE during treatment with the green tea extract essentially reflects its stimulatory effect on thermogenesis. Furthermore, despite the absence of differences in urinary nitrogen excretion, and hence in protein oxidation rates, the observed reductions in RQ during treatment with the green tea extract suggest that fat oxidation was higher and carbohydrate oxidation was lower during this period than during the placebo period. Indeed, calculations of the relative contribution of substrate oxidation to daily EE indicated that the contribution of fat oxidation to 24-h EE, which was 31.6% with the placebo, was higher (41.5%) with the green tea extract. Of particular interest in this study was that the effects of the green tea extract in enhancing thermogenesis and fat oxidation could not be explained solely on the basis of its caffeine content because treatment with an amount of caffeine equivalent to that in the extract failed to alter EE, RQ, or substrate oxidation. The implication of this finding is that these metabolic effects resulted from ingredients other than caffeine in the green tea extract. The most likely explanation for the lack of a thermogenic effect of caffeine is that the dosage (50 mg 3 times/d) was below the threshold for stimulating thermogenesis. On the basis of data from the literature, a single oral dose of ≥ 100 mg caffeine is required to produce a thermogenic response sustainable for ≥ 1 –2 h, and a stimulatory effect of caffeine per se on 24-h EE under respiratory chamber conditions has only

been reported with dosages of 600–1000 mg caffeine/d (18, 19). It is therefore not surprising that in the present study, the administration of caffeine alone (< 100 mg with each meal) failed to increase daily EE. Nonetheless, the amount of caffeine consumed during treatment with the green tea extract may have reached the critical dose, which, although ineffective by itself, may have enabled a synergistic interaction with other bioactive ingredients in the green tea extract to promote catecholamine-induced thermogenesis and fat oxidation.

Mechanism of action

Green tea is well known for being particularly rich in flavonoids (14), and several of these polyphenols—particularly the subclass of flavonoids commonly known as tea catechins—have been shown in vitro to inhibit COMT (11), the enzyme that degrades norepinephrine. Given the important role of the SNS and its neurotransmitter norepinephrine in the control of thermogenesis and fat oxidation, it is conceivable that these catechins, by inhibiting COMT, result in an increase in or a more prolonged effect of norepinephrine on thermogenesis and fat metabolism or both. Support for this contention comes from our previously reported in vitro studies on the respiration rate of brown adipose tissue, which indicated that 1) a green tea extract (rich in catechin polyphenols and to a lesser extent in caffeine) was more potent than were equimolar concentrations of caffeine alone in stimulating the respiration rate of brown adipose tissue (12), 2) the thermogenic effect of a green tea extract was markedly potentiated by enhancing the release of norepinephrine from the sympathetic nerve terminals with the use of ephedrine (12), and 3) the thermogenic effect of a green tea extract could be mimicked by epigallocatechin gallate (20). Furthermore, the assay of urinary catecholamines in the present study of humans showed a tendency for urinary norepinephrine (and its precursor dopamine), but not for epinephrine, to be higher in most subjects during treatment with the green tea extract; however, differences across treatments were only significant for total 24-h norepinephrine excretion. This observation is consistent with the inhibiting effect of green tea on COMT, the consequential reduction in norepinephrine degradation, and hence, the spillover of norepinephrine into the circulation, thereby accounting for the higher urinary excretion of norepinephrine. Such effects, resulting in a prolonged life of norepinephrine in the sympathetic synaptic cleft, could explain the observed effects of the extract in stimulating thermogenesis and fat oxidation.

It can be argued, however, that other tea flavonoids—such as quercetin and myricetin, which have also been shown to inhibit COMT in vitro (11)—may also have played a role in the metabolic effects of the green extract observed in the present study. However, there are only minute amounts of these flavonoids in green tea and their absorption when taken orally is doubtful, par-

TABLE 3

Substrate oxidation during 24 h in the respiratory chamber¹

	Placebo	Caffeine	Green tea	P ²
Protein				
(g)	65.6 ± 3.1	66.9 ± 4.7	68.3 ± 3.5	NS
(% of 24-h EE)	13.2 ± 1	13.4 ± 0.98	13.3 ± 0.98	NS
Carbohydrate				
(g)	336 ± 16	324 ± 16	285 ± 17 ¹	<0.001
(% of 24-h EE)	55.1 ± 2.4	52.7 ± 2.1	45.2 ± 2.7 ¹	<0.001
Fat				
(g)	76.2 ± 10.6	81.9 ± 8.7	103 ± 13 ¹	<0.001
(% of 24-h EE)	31.6 ± 3.1	33.8 ± 2.4	41.5 ± 3.1 ¹	<0.001

¹ $\bar{x} \pm \text{SEM}$; $n = 10$.² For differences across treatments (ANOVA).³ Significantly different from placebo, $P < 0.05$ (post hoc pairwise comparison with Tukey's test).⁴ Significantly different from placebo and caffeine, $P < 0.05$ (post hoc pairwise comparison with Tukey's test).

TABLE 4

Urinary catecholamines during diurnal, nocturnal, and total 24-h periods¹

	Placebo	Caffeine	Green tea	P ²
	nmol			
Diurnal				
Epinephrine	66 ± 16	49 ± 4	55 ± 7 ¹	NS
Norepinephrine	106 ± 15	127 ± 24	146 ± 23 ¹	NS
Dopamine	893 ± 173	946 ± 160	1086 ± 179 ¹	NS
Nocturnal				
Epinephrine	12 ± 4	19 ± 4	15 ± 3 ¹	NS
Norepinephrine	54 ± 5	61 ± 11	73 ± 7 ¹	NS
Dopamine	694 ± 80	632 ± 126	803 ± 105 ¹	NS
Total 24 h				
Epinephrine	78 ± 13	67 ± 4	70 ± 8 ¹	NS
Norepinephrine	160 ± 14	187 ± 29	219 ± 27 ¹	<0.05 ⁴
Dopamine	1587 ± 187	1578 ± 165	1889 ± 241 ¹	NS

¹ $\bar{x} \pm \text{SEM}$; $n = 10$.²For differences across treatments (ANOVA).³Significantly different from placebo, $P < 0.05$ (post hoc pairwise comparison with Tukey's test).⁴ $F = 3.96$.

ticularly because of evidence that flavonoids in food cannot generally be absorbed from the small intestine because they are bound to sugars as glycosides. By contrast, catechins are not only present in large quantities in green tea, but they are known to be better absorbed than are flavonoids. Indeed, substantial amounts of epigallocatechin gallate, epigallocatechin, and epicatechin have been measured in the plasma of human volunteers after ingestion of green tea powder, with peak plasma concentrations of catechins (nonconjugated) after 3 h of 3–3% of the ingested dose (21, 22). It is not known whether the relatively low ratios of circulating catechins to ingested catechins can be attributed to an efficient metabolism or to uptake by other tissues. However, the tissue concentrations of at least one of these tea catechins must have been high enough in our study to exert biological effects, as indicated by the stimulatory effect of the green tea extract on energy metabolism. Taken together, the results of these *in vitro* studies of rat brown adipose tissue thermogenesis (12) and *in vivo* studies of tea catechin bioavailability in humans (21, 22) suggest that the thermogenic effects of the green tea extract result, at least in part, from interactions between tea catechins, caffeine, and norepinephrine. The proposed mechanism is as follows: the catechins, by inhibiting COMT (and hence prolonging the life of norepinephrine in the synaptic cleft), and caffeine, by inhibiting phosphodiesterases (and hence prolonging the life of cAMP in the cell), result in an increase and more sustained effect of norepinephrine on thermogenesis.

Implications for weight control

First, the effect of the green tea extract on the metabolic rate represents an increase in 24-h EE of ~4%. It is likely that a major component of this increase in daily EE was due to a cumulative increase in postprandial thermogenesis during consumption of the 3 meals in the diurnal period, particularly because no significant differences in nocturnal EE were observed. If, as generally accepted, thermogenesis contributes 8–10% of daily EE in a typical sedentary man (760–950 kJ in our subjects), this 4% increase in 24-h EE (328 kJ) due to the green tea extract would extrapolate to a 35–43% increase in the thermogenesis compart-

ment of daily EE. This thermogenic effect of the extract (an increase of 328 kJ/d) was comparable with increases in daily EE seen in previous studies with much higher doses of caffeine in postobese and lean subjects (increases of 400 kJ) (18); however, only half of the thermogenic stimulation was the result of a combination of ephedrine and caffeine (800 kJ) (23). The results of these studies together with the results of our *in vitro* studies in brown adipose tissue—which indicate that the stimulatory effect of the extract on tissue thermogenesis was markedly potentiated in the presence of ephedrine (12, 20)—raise the possibility that the effect of the green tea extract could be greater under conditions of elevated sympathetic tone and norepinephrine release (ie, higher activity of COMT), such as during concomitant treatment with drugs that enhance norepinephrine release or when activity levels are higher than those under the confined and sedentary conditions of a respiratory chamber. Second, the differences in substrate utilization in favor of fat oxidation (lower RQ) in response to the green tea extract were much more consistent than were the differences in EE because lower RQs with the extract than with the placebo were observed in most of the subjects, including in those subjects who did not show a higher EE. This finding with the green tea extract is even more remarkable when compared with data indicating that caffeine ingestion alone, even at doses as high as 1000 mg/d, had no significant effect on the RQ during the diurnal or nocturnal period (19). Third, stimulation of thermogenesis and fat oxidation by the green tea extract was not accompanied by an increase in heart rate. In this respect, the green tea extract is distinct from sympathomimetic drugs, whose use as antiobesity thermogenic agents is limited by their adverse cardiovascular effects and, hence, are particularly inappropriate for obese individuals with hypertension and other cardiovascular complications.

Conclusion

In conclusion, oral administration of the green tea extract stimulated thermogenesis and fat oxidation and thus has the potential to influence body weight and body composition via changes in both EE and substrate utilization.

REFERENCES

1. Landsberg L, Young JB. Sympathoadrenal activity and obesity: physiological rationale for the use of adrenergic thermogenic drugs. *Int J Obes Relat Metab Disord* 1993;65:S29–34.
2. Dulloo AG. Strategies to counteract readjustments towards lower metabolic rates during obesity management. *Nutrition* 1993;9:366–72.
3. Arch JRS, Wilson S. Prospects for β_1 -adrenoceptor agonists in the treatment of obesity and diabetes. *Int J Obes Relat Metab Disord* 1996;20:191–9.
4. Dulloo AG. Spicing fat for combustion. *Br J Nutr* 1998;80:493–4.
5. Henry CJK, Emery B. Effects of spiced food on metabolic rate. *Hum Nutr Clin Nutr* 1986;40C:165–8.
6. Yoshioka M, St-Pierre S, Suzuki M, Tremblay A. Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. *Br J Nutr* 1998;80:503–10.
7. Dulloo AG. Ephedrine, xanthines and prostaglandin-inhibitors: actions and interactions in the stimulation of thermogenesis. *Int J Obes Relat Metab Disord* 1993;17:S35–40.
8. Toubro S, Astrup A, Broun L, Quaade F. Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. *Int J Obes Relat Metab Disord* 1993;17:S69–72.

9. Dulloo AG, Seydoux J, Girardier L. Potentiation of the thermogenic antiobesity effects of ephedrine by dietary methylxanthines: adenosine antagonism or phosphodiesterase inhibition? *Metabolism* 1992;41:1233-41.
10. Durand J, Giacobino JP, Girardier L. Catechol-O-methyl-transferase activity in whole brown adipose tissue of rat in vitro. In: Girardier L, Seydoux J, eds. *Effectors of thermogenesis*. Basel, Switzerland: Birkhauser, 1977:45-53.
11. Borchardt RT, Huber JA. Catechol-O-methyltransferase: structure-activity relationships for inhibition by flavonoids. *J Med Chem* 1975;18:120-2.
12. Dulloo AG, Seydoux J, Girardier L. Tealine and thermogenesis: interactions between polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord* 1996;20(suppl):71(abstr).
13. Durnin JVG, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness measurements of 481 men and women aged 16-72 years. *Br J Nutr* 1974;32:77-97.
14. Stagg GV, Millin DJ. The nutritional and therapeutic value of tea—a review. *J Sci Food Agric* 1975;26:1439-59.
15. Cunningham JJ. Body composition as a determinant of energy expenditure: a synthetic review and a proposed general prediction equation. *Am J Clin Nutr* 1991;54:963-9.
16. Dulloo AG, Fathi M, Mensi N, Girardier L. Twenty-four hour energy expenditure and urinary catecholamines of humans consuming low-to-moderate amounts of medium-chain-triglycerides: a dose-response study in a respiratory chamber. *Eur J Clin Nutr* 1996;50:152-8.
17. Jequier E, Acheson KJ, Schutz Y. Assessment of energy expenditure and fuel utilization in man. *Annu Rev Nutr* 1987;7:187-208.
18. Diniton AG, Grissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and post-obese human volunteers. *Am J Clin Nutr* 1989;49:44-50.
19. Brucco D, Ferrara JM, Arnaud MJ, Jaquier E, Schutz Y. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. *Am J Physiol* 1995;269:E671-8.
20. Dulloo AG, Seydoux J, Girardier L, Chénier P, Vandermander J. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord* (in press).
21. Lee MJ, Wang ZY, Li H, et al. Analysis of plasma and urinary tea polyphenols in human subjects. *Cancer Epidemiol Biomarkers Prev* 1995;44:393-9.
22. Hollman PCH, Tijburg LBM, Yang CS. Bioavailability of flavonoids from tea. *Crit Rev Food Sci Nutr* 1997;37:719-38.
23. Dulloo AG, Miller DS. The thermogenic properties of ephedrine/methylxanthine mixtures. human studies. *Int J Obes* 1986;10:467-81.



The American Journal of Clinical Nutrition

Official Journal of The American Society for Clinical Nutrition

9650 Rockville Pike, Bethesda, MD 20814-3998

(301) 530-7038 Fax (301) 571-8303

WWW.AJCN.ORG